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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,849	VELANDER, WILLIAM HUGOLD	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-31,33,35,36,40-44,46,50,53 and 55-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-31,33,35,36,40-44,46,50,53 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the First Action of February 2, 2005 on June 3, 2005. Applicant has also filed a response to a Non-Compliant amendment to Claims filed June 3, 2005 on September 14, 2005.

Claims 1, 5-8, 11-13, 16, 17, 20, 22, 24, 25, 27, and 53 are withdrawn. Claims 2-4, 9, 10, 14, 15, 18, 19, 21, 23, 26, 32, 34, 37-39, 45, 47-49, 51, 52, 54 are cancelled. Claims 56-58 are new.

Claims 28-31, 33, 35, 36, 40-44, 46, 50, 55-58 are under consideration.

Withdrawn Rejections

Provisional Double Patenting

Applicant's arguments, see page 9 of Applicant's response, filed June 3, 2005, with respect to the Provisional Double Patenting rejection of claims 28, 40, 50 have been fully considered and are persuasive. Applicant has amended the claims. The rejection of claims 28, 40, 50 has been withdrawn.

35 U.S.C. § 102

Applicant's arguments, see pages 7-9, filed June 3, 2005, with respect to the rejection of claims 28, 40, 50 under 35 U.S.C. § 102(e), as being anticipated by Application 10/062,447 have been fully considered and are persuasive. Applicant has amended the claims. The rejection of claims 28, 40, 50 has been withdrawn.

Applicant's arguments, see pages 7-9, filed June 3, 2005, with respect to the rejection of claims 28-30, 33, 35,36, 38, 40-42, 44, 46, 48, 55 under 35 U.S.C § 102(b), as being anticipated by Holly et al. have been fully considered and are persuasive. Applicant has amended the claims. The rejection of claims 28-30, 33, 35, 36, 38, 40-42, 44, 46, 48, 55 has been withdrawn.

Applicant's arguments, see pages 7-9, filed June 3, 2005, with respect to the rejection of claims 28-30, 40-42, 50, 55 under 35 U.S.C. § 102(b) as being anticipated by Lee et al. have been fully considered and are persuasive. Applicant has amended the claims. The rejection of claims 28-30, 40-42, 50, 55 has been withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-31, 33, 35, 36, 40-44, 46, 50, 55-58 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The specification generally provides guidance that prothrombin is processed into thrombin by two cleavage events (specification, page 2, 3rd parag.), and that prothrombin and thrombin exhibit a variety of posttranslational modifications, including glycosylation and glutamic acid gamma-carboxylation (specification, pages 3-4). The specification teaches that human and bovine prothrombin are gamma-carboxylated at glutamic acid residues 7, 8, 15, 17, 20, 21, 26, 27, 30, and 33 and rat and mouse likely

have the same pattern as well. The specification indicates that some of the residues are required for calcium-dependent membrane binding and that other residues modulate interaction and complex formation of prothrombin with other vitamin K-dependent coagulation factors. The specification teaches that in particular for humans, it appears that complete carboxylation is required for activation and conversion of prothrombin to thrombin. The specification indicates that the extent of gamma-carboxylation of prothrombin varies markedly from one preparation to another, even for preparations made in the same system, according to the same protocol (specification, page 3, 2nd parag.). With regards to glycolsylation, the specification teaches that human prothrombin contains three sites for N-linked glycosylation (Asn-27, Asn-101, and Asn-378), like human, is glycosylated at 3 sites, but the sites are Asn-77, Asn-101, Asn-378. The specification teaches that mouse and rat prothrombin is glycosylated at 5 sites. The specification teaches that glycosylation plays an important role in activity and physiological function and effects of prothrombin. Generally, glycosylation can affect enzymatic activity, substrate preferences, binding to cofactors, and other moieties, complex formation, thermal stability, resistance to proteases and physiological persistence (specification, page 3, 4th parag. to page 4, 2nd parag.). While the specification provides general guidance on these post-translational modifications and generally indicates some of the biological effects that would result from changes in post-translational modification, the specification does not provide the correlation between the structures of domains or regions of prothrombin/thrombin and the effect(s) these changes have on prothrombin/thrombin biological activity, such that an artisan would

know what structures of prothrombin/thrombin to maintain such that specific activity of prothrombin/thrombin to a specific reagent would be maintained or predictably changed. It is noted with particular attention to glycosylation, that there are differences in glycosylation patterns between rat, mouse, bovine, and human prothrombin. It is unclear what about the changes in glycosylation patterns amongst these proteins would cause changes in enzymatic activity, thermal stability, resistance to proteases, and physiological persistence. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, while the specification indicates post-translational modifications that generally affect the activity of prothrombin, and generally indicates that certain domains or regions or prothrombin affect the proteins biological activity, the specification does not provide guidance as to what structures/characteristics of prothrombin is common amongst the family of prothrombins, such that an artisan could predictably obtain any prothrombin family member and predictably cause changes in enzymatic activity, thermal stability, resistance to proteases, and physiological persistence. The skilled artisan cannot envision all the possible variant modifications

(glycosylation, gamma-carboxylation, and proteolytic processing) that one could apply to any prothrombin family member and know the resultant biological effects from that modification, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, no prothrombin or thrombin meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 28-31, 33, 35, 36, 40-44, 46, 50, 55-58 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention is drawn to a recombinant polypeptide that comprises a Gla domain and a region that is at least 70% identical to human prothrombin, a recombinant polypeptide comprising human thrombin, a composition comprising either prothrombin or thrombin, and a method for making said recombinant prothrombin or thrombin. The issues regarding enablement are raised as follows.

The primary issue that is being raised in the enablement rejection is similar to that of the written description, discussed above. When considering the enablement of

the claimed invention, an artisan would need to consider the intended use of the claimed invention. The specification indicates that the claimed invention has clinical applications including promoting hemostasis, improving anastomoses, and controlling hemorrahaging (specification, pages 4-5). Based on this intended use, the prothrombin and thrombin molecules envisioned in the claimed invention are ones that have activity. The claims broadly encompass various forms and portions of recombinant prothrombin/thrombin, that is, polypeptides that "differ" in post-translational modification from a "naturally occurring" human prothrombin (e.g. see claim 29). While the specification provides general guidance as to the general structure of prothrombin, indicates that prothrombin undergoes post-modification processing, and that generally post-modification processing affects the maturation of prothrombin to thrombin or affects the biological activity of thrombin, the specification does not give specific guidance as to what are the structures or characteristics of a "naturally occurring" prothrombin/thrombin has such that an artisan would know that recombinant prothrombin/thrombin would have a structure that is different from that of the "naturally occurring" one. In addition to this, nothing in the specification provides guidance as to what structures/characteristics an artisan would need to maintain in prothrombin/thrombin, such that an artisan could predictably arrive at a functional prothrombin/thrombin. As such, it is unclear from the specification what "differences" occur between "naturally occurring" prothrombin/thrombin and it is unclear what specific residues, structures, post-modifications would need to be conserved such that an artisan could obtain a functional prothrombin/thrombin such that it is encompassed by the claims. For example, the

specification teaches that two cleavage reactions occur in order to process prothrombin to active thrombin (specification, page 2, 3rd parag.). However, nothing in the specification indicates other cleavage patterns or that removing cleavage sites result in active thrombin protein. In the case of gamma-carboxylation, the specification teaches that complete carboxylation is required for activation and conversion of prothrombin to thrombin (specification, page 3, 3rd parag). If this is the case, then incomplete carboxylation, a different post-translational modification from a naturally occurring human prothrombin, would not have activity. Nothing in the specification has thus indicated that different modifications of gamma-carboxylation of human prothrombin could be used. In the case of glycosylation, the specification indicates that mouse, rat, bovine, and human prothrombin have different glycosylation patterns. In addition to this, the specification teaches that glycosylation has an important role in activity and physiological function of prothrombin (specification, page 4). The specification generally teaches that glycosylation affects enzymatic activity, substrate preferences, binding to cofactors and other moieties, complex formation, thermal stability, resistance to proteases, and physiological persistence. However, nothing in the specification teaches that specific regions, structures, or post-modifications in thrombin or prothrombin would need to be conserved in order to obtain thrombin that has enzymatic activity, substrate preferences, can bind to cofactors and other moieties, participates in complex formation, has thermal stability, is resistant to proteases, and has physiological persistence. As such, the specification, as filed, does not provide sufficient guidance to practice the claimed invention.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-31, 33, 35, 36, 40-44, 46, 50, 55-58 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28, 40, 55 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 28, 40, 55 are unclear because they use the word, "transgenic," to describe a polypeptide. According to dictionary.com, transgenic means, "Of, relating to, or being an organism whose genome has been altered by the transfer of a gene or genes from another species or breed: *transgenic mice; transgenic plants,*" and is used to describe an organism, and not a polypeptide. Claims 29-30, 33, 35, 36, 41-44, 46, 50, 55-58 depend on claims 28, 40, 55.

Claims 28, 33, 36, 40, 44, 55 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 28, 33, 36, 40, 44, 55 use the word, "region" to describe a part of human prothombin or thrombin. However, the metes and bounds of this word are unclear because there are no upper and lower

limits as to what comprises a "region." Claims 29-30, 35, 36, 41-43, 46, 50, 56-58 depend on claims 28, 33, 36, 40, 44, 55.

Claims 28, 33, 36, 40, 44, 55 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 28, 33, 36, 40, 44, 55 use the word, "identical." The metes and bounds of this word is unclear because it is unclear if "identical" refers to the amino acid and/or the location of the amino acid in the protein. Claims 29-30, 35, 36, 41-43, 46, 50, 56-58 depend on claims 28, 33, 36, 40, 44, 55.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28, 31, 33, 35, 36, 40, 42, 43, 44, 46, 50, 56, 58 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Le Bonniec et al., 1991, JBC, 266: 13796-13803.

Le Bonniec et al. teach two expression vectors. One vector comprised a nucleic acid sequence encoding human prothrombin and a second vector comprised a nucleic acid sequence encoding human prothrombin comprising a glutamine to lysine substitution at amino acid 39 (E39K) (Le Bonniec et al., page 13797, under Materials

and Methods, "DNA Manipulations"). Le Bonniec et al. teach that the expression vectors were introduced to BHK-21 (baby hamster kidney cells) and recombinant prothrombin was expressed and purified to homogeneity (Le Bonniec et al., 13798, 2nd col. under Results, "Preparation of the Recombinant Thrombins"). Le Bonniec et al. teach that the wild type and mutated recombinant prothrombins were activated by bovine factor Xa, in the presence of bovine factor Va, phospholipids, and calcium (Le Bonnic et al., page 13799, 1st col., 2nd parag.).

Thus, Le Bonniec et al. anticipate claims 28, 31, 33, 35, 36, 40, 42, 43, 44, 46, 50, 56, 58.

Claim 50 is drawn to a polypeptide produced in milk. It is anticipated because patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). As such, while the claim comprises an embodiment that the polypeptide be produced in milk, the composition, regardless of how it was made, is anticipated by Le Bonniec.

Claims 28-31, 33, 35, 36, 40-44, 46, 50, 56, 58 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al. 1997, PNAS, USA, 94: 13654-13660.

Wu et al. teach that vitamin K antagonists, such as warfarin, inhibit the vitamin-K-dependent γ-glutamyl carboxylation during protein processing and block the secretion of under γ-carboxylated prothrombin (FII) in rat, but not in the human or bovine (Wu et al., abstract). Wu et al. teach that the differential response is determined by the structural difference in the proteins, rather than by the origin of the cell line that expresses recombinant prothrombin (Wu et al. abstract). In order to determine the structural signal required for the differential response, chimeric cDNAs with the propeptide/Gla domains, kringle domain, and serine protease domains were exchanged between rat FII and human FII (FII_{RHH} and FII_{HRR}, FII_{RRH} and FII_{HHR}, FII_{FHF} and FII_{HRH}) and expressed in both warfarin-treated HEK293 cells and HepG2 cells (Wu et al., pages 13654-13655, Materials and Methods, under "Chimeric cDNA Constructs" and "Cell Culture and Transfections"). Wu et al. teach that the C-terminal catalytic domain constitutes more than 50% of the prothrombin molecule, and prothrombin from rat and human shares about 86% amino acid sequence identity in this region (Wu et al., page 13659, 1st col., 2nd parag.). In addition to this, Wu et al. teach that there is an 86% amino acid identity between rat and human propeptide and Gla domains (Wu et al., page 13659, 1st col., 2nd parag. to 2nd col., 1st parag.).

Wu et al. thus anticipate claims 28-31, 33, 35, 36, 40-44, 46, 50, 56, 58. It is noted that the difference in post-translational modification (claims 29 and 40) is under γ-carboxylation.

Claim 50 is drawn to a polypeptide produced in milk. It is anticipated because patentability of a product-by-process claim is determined by the novelty and

nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). As such, while the claim comprises an embodiment that the polypeptide be produced in milk, the composition, regardless of how it was made, is anticipated by Wu et al.

Claims 28-31, 33, 35, 36, 40-44, 46, 50, 56, 58 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Cote et al., U.S. Patent 5,510,248, patented April 23, 1996, filed June 22, 1993 and as evidenced by Deguchi et al., 1997, Biochem J., 321: 729-735.

Cote et al. teaches two novel meizothrombin-like molecules with anti-coagulant activity (Cote et al., col. 3 under Detailed Description of the Invention). Both polypeptides have the amino acid sequence of human prothrombin with amino acid substitutions at argentine residues 155, 271, and 284. These mutations disrupt two thrombin and one factor Xa cleavage sites so that they are not recognized by these specific proteases. (It is noted that the there are 622 amino acids in the sequence of human prothrombin, NCBI Accession Number ACC64065. 3 amino acid substitutions in human prothrombin would make this prothrombin 99.5% identical to human prothrombin.) Cote et al. teach that these mutations alter the activity of the activated molecule (rhMZa) in that it greatly reduces its procoagulant activity toward fibrinogen (to

about 7% of that of prothrombin), but does not alter its anticoagulant activity toward protein C (Cote et al., col. 3, line 63 to col. 4, line 7). Cote et al. teach that rhMZa can be activated by the snake venom activator ecarin or by naturally occurring prothrombinase complex (Cote et al., col. 4, lines 9-13). The second polypeptide has an additional amino acid substitution at residue 320. (It is noted that 4 amino acid substitutions in human prothrombin would make this prothrombin 99.3% identical to human prothrombin.) This polypeptide, rhQM, disrupts all the proteolytic cleavage sites in the protein and renders rhQM resistant to activaton. Cote et al. teach that wild type recombinant human prothrombin was expressed using the pNUT expression vector and BHK (baby hamster kidney) cells. One cell line secreted approximately 200ug/ml or recombinant prothrombin into the culture medium. Upon activation of the purified recombinant prothrombin with the prothrombinase complex, however, incomplete activation was observed, consistent with under γ-carboxylation of the recombinant protein (Cote, et al., col. 11-12, Example 2). Cote et al. also teach that rMZ was expressed in BHK cells. Cote et al. teach that the highest expressing clone was cultured and about 20ug/ml of rMZ was detected (Cote et al., col. 12, 2nd parag).

Thus, Cote et al. anticipate claims 28-31, 33, 35, 36, 40-44, 46, 50, 56, 58. With regards to the issue that the prothrombin be proteolytically processed by Factor Xa, Faxtor Va, calcium, and phospholipids (claim 58), Deguchi et al. (1997) teach that the prothrombinase complex is comprised of Factor Xa, Factor Va, negatively charged phospholipids, and calcium ions (Deguchi et al., abstract). With regards to the recombinant transgenic polypeptide comprising a Gla domain and a region that is at

least 70% identical to human prothrombin and having a specific activity between 50% to 150% of a purified human prothrombin, Cote et al. teach that the anticoagulant activity of rhMZa to protein C is not altered. According to the online cell biology laboratory manual provided by Dr. Heidcamp at Gustavus Aldolphus College (see website printout), specific activity is defined in terms of enzyme units per mg enzyme protein. An enzyme unit is the amount of substrate converted to product per unit time under specific reaction conditions for pH and temperature. Thus, according to this definition, because Cote et al. teach that the processing of protein C by rhmZA is not changed, it indicates that the specific activity of rhmZA, when using protein C as a substrate, is not changed, and has a specific activity 100% of that of wild type prothrombin.

Claim 50 is drawn to a polypeptide produced in milk. It is anticipated because patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). As such, while the claim comprises an embodiment that the polypeptide be produced in milk, the composition, regardless of how it was made, is anticipated by Cote et al.

Claims 28, 29, 30, 31, 33, 35, 36, 40-44, 46, 50 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Wu and Suttie, 1999, Thrombosis Research, 96: 91-98 as evidenced by Wu et al. 1997, PNAS, USA, 94: 13654-13660.

Wu and Suttie teach that rat prothrombin (rFII) was expressed in H-35 (hepatoma) cells in the presence of tunicamycin. The expression constructs used to express the recombinant proteins are described (Wu and Suttie, page 92, under "1.2. Site-Directed Mutagenesis and Construction of Expression Plasmids"). Rat prothromin treated with tunicamycin demonstrated greater mobility on an SDS-PAGE gel (Wu and Suttie, Figure 1) than a glycosylated rFII synthesized in the absence of tunicamycin. However, aglyco-rFII was secreted efficiently only in the presence of vitamin K, while the secretion of aglyco-rFII was abolished by warfrain treatment (Wu and Suttie, page 93, under "2.1. Degradation of aglyco-rFII in Warfarin-treated H-35 Cells"). In addition to teaching the changes in glycosylation on rFII in the presence of tunicamycin, Wu and Suttie teach that human prothrombin (hFII) was aglycosylated when cells comprising the hFII construct was cultured in the presence of tunicamycin (e.g. see Wu and Suttie, Figure 7).

Thus Wu and Suttie anticipate claims 28, 29, 30, 31, 33, 35, 36, 40-44, 46, 55. It is noted that claims 28, 36, 46, 55 are drawn to a polypeptide, wherein the amino acid sequence has a percentage of identity to human thrombin. According to Wu et al. (1997), the rat and human prothrombin catalytic domain shares about 86% amino acid sequence identity. Also, the propeptide and Gla domains between human and rat

prothrombin have an 86% amino acid identity (Wu et al., page 13659, 1st col., 2nd parag. to 2nd col. 1st parag.).

Claim 50 is drawn to a polypeptide produced in milk. It is anticipated because patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). As such, while the claim comprises an embodiment that the polypeptide be produced in milk, the composition, regardless of how it was made, is anticipated by Wu and Suttie.

Claims 28, 29, 30, 33, 35, 36, 40, 41, 42, 44, 46, 50 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Wu and Suttie, 1999, Thrombosis Research, 96: 91-98.

Wu and Suttie teach that there are differences in glycosylation patterns in human and rat prothrombin (hFII and rFII). There are four potential N-glycolylation sites in hFII (Asn79, Asn101, Asn165, Asn 378), but only three are used for glycolylation Asn79, Asn101, and Asn378. In the case of rat, rFII has five potential N-glycolsylation sites at positions 77, 101, 165, 378, and 518. Three of these sites (Asn77, Asn101, and Asn165) are used (Wu and Suttie, page 92, 1st col., 2nd parag.).

Thus, Wu and Suttie anticipate claims 28, 29, 30, 33, 35, 36, 40, 41, 42, 44, 46, 50. It is noted that Wu and Suttie teach that there are naturally occurring differences in glycosylation patterns in rFII and hFII.

Claim 50 is drawn to a polypeptide produced in milk. It is anticipated because patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). As such, while the claim comprises an embodiment that the polypeptide be produced in milk, the composition, regardless of how it was made, is anticipated by Wu and Suttie.

Claims 28, 33, 36, 40, 42, 44, 50, 57 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Seegers, et al., 1950, Blood, 5: 421-433 as evidenced by an National Center for Biolechnology Information (NCBI) BLAST search for bovine prothrombin.

Seegers et al. teach how to prepare prothrombin. The steps briefly comprise of diluting especially oxalated bovine plasma 16-fold and acidifying to pH 5.1. The precipitate is dissolved in oxalated saline and the prothrombin is adsorbed on magnesium hydroxide, from which it can be eluted by decomposing the hydroxide with carbon dioxide. The eluate is fractionated with concentrated ammonium sulfate and the

prothrombin is finally precipitated from aqueous solution near the isoelectric point (Seegers et al., page 422, under "Preparation of Prothrombin"). Seegers teach that activation of purified prothrombin is accomplished by dissolving the purified prothrombin in a 25% solution of sodium citrate and allowing the mixture to stand at room temperature. After about 5 hours, measurable amounts of thrombin appear (Seegers, et al., page 421, 3rd parag.).

Thus, Seegers et al. anticipate claims 28, 33, 36, 40, 42, 44, 50, 57. It is noted that the BLAST search had indicated that there is an 81% amino acid sequence identity between bovine and human prothrombin sequences (see NCBI webpage printout).

Claim 50 is drawn to a polypeptide produced in milk. It is anticipated because patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). As such, while the claim comprises an embodiment that the polypeptide be produced in milk, the composition, regardless of how it was made, is anticipated by Seegers et al.

Claims 28, 33, 36, 40, 42, 44, 50, 57 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Vogel et al. 1976, Biochemistry, 15: 3265-3269.

Vogel et al. teach that bovine prothrombin activation reactions were performed under ambient conditions in either 0.05 M Tris, pH 8.0 or 0.05 M sodium phosphate, pH 8.0. Prothrombin, factor Xa, and polylysine were added as solutions in 0.05 M Tris, pH 8.0 (Vogel et al., page 3266, 1st col., 2nd parag.). Vogel et al. teach the effects of polylysine concentration on the activation of prothombin by factor Xa (Vogel et al., Figure 1).

Thus, Vogel et al. anticipate claims 28, 33, 36, 40, 42, 44, 50, 57.

Claim 50 is drawn to a polypeptide produced in milk. It is anticipated because patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). As such, while the claim comprises an embodiment that the polypeptide be produced in milk, the composition, regardless of how it was made, is anticipated by Vogel et al.

Claims 28, 33, 36, 40, 42, 44, 50, 57 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Landaburu and Seegers, 1958, Am. J. Physiol. 193: 169-180.

Landaburu and Seegers teach that in experiments with purified bovine biothrombin, it was found that strong solutions of sodium citrate or protamine sulfate (0.1% w/v) or purified platelet factor 3 depress the esterase activity and leave the

clotting power unaltered. Apparently, a depression of esterase activity is beneficial for the autocatalytic activation of purified prothrombin (Landaburu and Seegers, abstract).

Thus, Landaburu and Seegers anticipate claims 28, 33, 36, 40, 42, 44, 50, 57.

Claim 50 is drawn to a polypeptide produced in milk. It is anticipated because patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). As such, while the claim comprises an embodiment that the polypeptide be produced in milk, the composition, regardless of how it was made, is anticipate by Landaburu et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40, 50, 55 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Morcol and Bell, U.S. Patent 6,183,803 B1, patented February 6, 2001, filed June 11, 1999.

Morcol and Bell teach that expression of recombinant proteins can be targeted to a particular tissue, such as the mammary gland (U.S. Pat. Nos. 5,565,362 and 5,589,604. Mammary expression provides a highly efficient system for the synthesis and secretion of large quantities of recombinant proteins. A number of biologically active human proteins in transgenic milk have been reported (Morcol and Bell, col. 1, 4th parag. under Background of the Invention). While Morcol and Bell do not explicitly teach recombinant prothrombin expressed in milk of a transgenic mammal, they do teach that therapeutic agents, such as prothrombin, is one protein that could be expressed in milk of transgenic mammals (Morcol and Bell, col., 6, line 4).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express prothrombin into the milk of a transgenic mammal.

One having ordinary skill in the art would have been motivated express prothrombin, a therapeutic protein, into the milk of a transgenic mammal, in order to obtain large quantities of active, recombinant prothrombin.

There would have been a reasonable expectation of success given that Morcol and Bell provide examples of other artisans who use a transgenic mammal as a bioreactor to obtain active transgenic proteins, such as human lactoferrin, protein C, tissue-type plasminogen activator (tPA), and alpha-1-antitripsin (α1-AT).

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH